PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/011963	21.10.2004	24.10.2003

International Patent Classification (IPC) or both national classification and IPC
C07C275/32, C07C279/18, C07C217/60, C07C233/25, C07C235/42, C07C255/54, C07D213/82, C07D307/68,

Applicant
GLAXO GROUP LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-10

because:

☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-10 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☒ the claims, or said claims Nos. 1-10 are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-10

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-9,11-15
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Present claims 1-15 relate to an extremely large number of possible compounds due to the fact that the term "physiologically functional derivatives" is vague and imprecise and leaves the skilled person in the art in doubt about the subject-matter for which protection is sought. For this reason lack of clarity within the meaning of Art. 6 PCT arises to such an extent as to render a meaningful search and a meaningful examination of the claims impossible. Furthermore, support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search and examination over the whole of the claimed scope are impossible. Consequently, the search and the examination have been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formulae (I) /(Ia) and their salts and solvates, as well as the use and the preparation of these compounds, salts and solvates.

   The applicant's attention is drawn to the fact that the claims or parts of claims, relating to inventions in respect of which no internal search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examination Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

2. For the assessment of the present claim 10 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO 03/091204 A (GLAXO GROUP LIMITED; BOX, PHILIP, CHARLES; COE, DIANE, MARY; LOOKER, B) 6 November 2003 (2003-11-06)

D2: WO 2004/039766 A (GLAXO GROUP LIMITED; BIGGADIKE, KEITH; BLAKE, KEITH; COE, DIANE, MARY;) 13 May 2004 (2004-05-13)

D3: WO 2004/037773 A (GLAXO WELLCOME HOUSE; CHAPMAN, ALAN, MICHAEL; GUNTRIP, STEPHEN, BARRY;) 6 May 2004 (2004-05-06)

D4: WO 2004/071388 A (GLAXO GROUP LIMITED; BIGGADIKE, KEITH; BOX, PHILIP, CHARLES; COE, DIAN) 26 August 2004 (2004-08-26)

D5: APPERLEY G H ET AL: "Selectivity of Beta-adrenoceptor agonists and antagonists on bronchial, skeletal, vascular and cardiac muscle in the anaesthetized cat" 1976, BRITISH JOURNAL OF PHARMACOLOGY, BASINGSTOKE, HANTS, GB, PAGE(S) 235-246 , XP000926140 ISSN: 0007-1188

D6: US-A-4 992 474 (SKIDMORE ET AL) 12 February 1991 (1991-02-12)

D7: IAKOVIDIS D ET AL: "Synthesis and beta-adrenoceptor agonist properties of (+/-)-1-(3',4'-dihydroxyphenoxy)-3-(3",4' '-dimethoxyphenyl) ethylamino-2-propanol hydrochloride, (+/-)-RO363.HCl, and the (2S)-(-)-isomer" June 1999 (1999-06), EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, PAGE(S) 539-548 , XP004180361 ISSN: 0223-5234

1. The present application relates to phenethanolamine derivatives (I) or salt or solvates thereof; a method for the prophylaxis or treatment of a clinical condition for which a selective beta2-adrenoreceptor is indicated, by administration of a compound according to formula (I); their use in medical therapy; pharmaceutical composition comprising a compound of formula (I); the use of compounds (I) in the preparation of medicaments for the treatment of a clinical condition for which a selective beta2-adrenoreceptor agonist is indicated and a process for the preparation of a compound (I).

2. D1-D4 disclose phenethanolamine derivatives very close in structure to the compounds disclosed in the present application; their use in the treatment of clinical conditions for

which a beta2-adrenoreceptor is indicated and methods for their preparation are disclosed as well (see the claims and the examples). The compounds in these documents differ from the compounds in the application either on the substitution of the phenyl substituent on the phenethanolamine moiety or in not having the phenyl substitution therein.

3. D5 discloses phenethanolamino derivatives which differ from those ones in the application only in the alkoxy substitution of the aryl moiety attached to the phenyl substituent of the phenethanolamine. These compounds are reported as selective beta-agonists (see specially table 1).

4. D6 discloses phenethanolamine derivatives useful as beta2-adrenoreceptor agonists which differ from those ones in the present application only in not having an aryl substituent on the phenethanolamine moiety (see the claims and the examples).

5. D7 discloses phenethanolamino derivatives which differ from those ones in the application only in the alkoxy substitution of the aryl moiety attached to the phenyl substituent of the phenethanolamine. These compounds are reported as selective beta-agonists (see specially pages 2, 3 and 4).

Novelty

6. The subject-matter of claims 1-15 is novel in the sense of Art. 33(2) PCT. None of the above-mentioned documents discloses compounds according to formula (I)/(Ia) in the application (see passages 3-5 herein). Hence, their use and methods for their preparation are novel as well.

Inventive step

7. The subject-mater of claims 1-15 cannot be considered to involve an inventive step in the sense of Art. 33(3) PCT.

7.1. Phenethanolamine derivatives useful as beta-adrenoreceptor agonists which differ from those ones in the application only in the alkoxy substitution of the aryl moiety attached

to the phenyl substituent of the phenethanolamine are known in the art; a range of alkoxy substituents on the phenyl moiety leading to active compounds is disclosed (see D5 and D7).

7.2. The problem to be solved in the application can be seen in view of the prior art in the provision of alternative beta-adrenoreceptor agonists.

7.3. The compounds proposed in the application are just a variation over the prior art of the substituent on the phenyl moiety attached to the phenethanolamine and taking into account that a) different substituents therein lead to active compounds (see D5 and D7) and b) the replacement of the phenyl moiety by a bond of an alkylen chain leads to active compound (D6), the minor modification carried out in the application over the prior art on the phenethanolamine moiety would be obvious for the skilled person in the art in order to provide alternative adrenoreceptor agonists.

7.4. An inventive step could only be acknowledged if comparative examples would have been provided showing that the technical feature in which differ the present claimed compounds form those ones known in the prior art -the phenyl moiety attached to the phenetanolamine moiety with its specific substitution- leads to an improvement (higher activity, selectivity) over the compounds in the closest state of the art. As a proof of such unexpected effects is not available at the moment, an inventive step cannot be acknowledged.

7.5. The attention of the applicant is drawn to the fact that a very broad variety of compounds are included in formula (I), specially due to the moiety Ar^1 whilst an evidence of activity is only provided for only very specific Ar^1 moieties leading therefore to a further objection of inventive step for the compounds according to formula (I). Furthermore, the compounds included in claim 1 differ from each other more than the compounds of the application from those ones disclosed in the prior art. Hence, after having dealt with the objection on paragraph 7.4, this objection has to be overcome.

Further comments

8. Claim 10 relates to subject-matter considered by this Authority to be covered by the

provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

9. The use of the term "physiologically functional derivatives" used in the claims and the description leads to lack of clarity about the subject-matter for which protection is sought, contrary to Art. 6 PCT and leads as well to lack of support and disclosure (Art. 6 and 5 PCT) as explained under item III above. Hence, this term should have been used neither in the description nor in the claims.

10. Claim 2 should have been drafted as dependant on claim 1.

11. Features introduced by terms like "preferably" and "such as" have no limiting effect on the scope of the claim including them (see Guidelines, C-III, 4.6). The presence of such non-limiting features is however detrimental to the conciseness of claims 1 and 10, contrary to Art. 6 PCT.

12. Claim 15 should have been drafted with an "or" between the possibilities (b) and (c) of the methods of preparation for compounds (I) in order to render the subject-matter of the claim clear (Art. 6 PCT).

13. The terms "hereby incorporated by reference" lead to lack of clarity about the subject-matter for which protection is sought, contrary to Art. 6 PCT. These terms should not have been used in the description.

14. The terms "the likes of" used in the description, for example on page 23 are vague and irriprecise, leading to lack of clarity about the subject-mater for which protection is sought, contrary to Art. 6 PCT.

15. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D7 is not mentioned in the description, nor are these documents identified therein.

16. Documents D1-D4 could become very relevant to assess the patentability of the present application when it enters the national/regional phase. No check has been made as to

whether the priority of the present application has been validly claimed.

17. When filing amended claims the applicant should at the same time bring the description into conformity with the amended claims.

18. In order to facilitate the examination of the conformity of the amended application with the requirements of Article 19(2) and 34(2) PCT, the applicant is requested to clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based.

    If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.